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Adenomatous polyp recurrence and physical activity in the Polyp Prevention Trial (United States)

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Abstract

Objective: To examine prospectively the association between physical activity and adenomatous polyp recurrence.
Methods: Information on past year total physical activity was collected annually through an interview-administered questionnaire from the 1905 men and women enrolled in a randomized dietary intervention study, the Polyp Prevention Trial. Multiple logistic regression analysis was used to examine the association between physical activity and polyp recurrence in up to three years of follow-up from baseline colonoscopy.
Results: There were no significant associations between moderate, vigorous, or total physical activity at the start of the trial and overall polyp recurrence in either men or women. Participants who reported consistent vigorous activity throughout the trial period had no significantly reduced risk of polyp recurrence compared to those who reported consistent sedentary activity (OR = 0.8, CI = 0.5–1.1). Consistent vigorous activity was also not significantly associated with either advanced or multiple polyps, nor with polyp recurrence at any specific anatomical location in the large bowel.
Conclusions: These prospective data suggest that recent physical activity is not associated with polyp recurrence in a three-year period.

Introduction

There is convincing evidence that higher activity levels are associated with a decreased risk of colon cancer; the data are more limited and less convincing for rectal cancer [1, 2]. Indeed, physical inactivity appears to be one of the risk factors most consistently associated with an increased risk of colon cancer [3]. Given the strong association with this disease, it would seem plausible that physical activity might also be associated with a decreased risk of adenomatous polpys, precursors of large-bowel cancer, and a reasonable intermediate marker often used in clinical trials [4].

To date one autopsy study, nine case–control studies, and two cohort studies have examined the association between physical activity and adenomatous polyps [5–16]. Of these 12 studies, eight have reported statistically significant inverse associations with one or more measures of physical activity [6–9, 11–14], while the other four, including one of the cohort studies, have reported modest or no associations [5, 10, 15, 16]. While the

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results to date have, in general, shown a protective association, many of the prior studies have certain limitations. A number of studies have used sigmoidoscopy and not colonoscopy results, thus limiting conclusions to the distal colon and rectum. Additionally, many of the physical activity measures have been limited, few have measured activity at more than one point in time, and many have assessed only occupational or recreational activity. This could be especially problematic for women, who may have a substantial proportion of their activity in household and childcare activities.

With the exception of one study, which looked at metachronous polyps [13], all prior studies have looked at prevalent, not necessarily incident, polyps. This type of design may be limited by the fact that the polyps may have already been present at the referent period of physical activity assessment. A different way to address this issue is to look at physical activity and polyp recurrence among people who have received cleaning colonoscopies, and are therefore free of polyps at the time of physical activity assessment. These different types of designs address different relationships between physical activity and polyps; the first examines the first known occurrence of polyps, and the latter the recurrence of polyps.

The Polyp Prevention Trial (PPT) is one setting in which to examine physical activity in the recurrence of polyps. This trial is a prospective study, identifying recurrence of large bowel polyps following a baseline cleaning colonoscopy with repeated measures of all types of physical activity. The purpose of the present study was to examine the association between reported levels of physical activity and colorectal polyp recurrence.

Methods

Study design and subjects

The PPT was a large multicenter, randomized, controlled trial of the effect of a diet low in fat and high in fiber, fruits, and vegetables on the recurrence of large-bowel adenomas. The study was a collaboration between eight study centers and was approved by the institutional review boards of the National Cancer Institute and each of the participating centers. All participants provided written informed consent. Full details of the study design and baseline characteristics of the subjects have been previously described [17, 18], as have the main trial results [19]. Briefly, subjects were at least 35 years old, had one or more histologically confirmed adenomas removed during a colonoscopy within six months of randomization, and had no history of colorectal cancer, surgical resection of adenomas, bowel resection, polyposis syndrome, or inflammatory bowel disease. These qualifying colonoscopies had to have been complete to the cecum, and any polyps found had to have been removed. Eligible subjects also weighed less than 150% of the recommended level (according to 1983 Metropolitan Life Insurance Tables), were taking no lipid-lowering drugs, and had no medical restrictions or dietary practices that would limit compliance with the protocol. A total of 2079 subjects were enrolled in the trial, with 1037 randomized to the intervention diet which was low in fat and high in fiber, fruits, and vegetables, while 1042 were randomly assigned to their usual diet. The study was completed by 958 subjects in the intervention group and 947 subjects in the control group.

Colonoscopy and adenoma assessment

Subjects returned to their usual endoscopist for colonoscopy at one year (T1) and four years (T4) after randomization. The one-year colonoscopy served to detect and remove any lesions missed at the baseline colonoscopy (T0). Data were obtained for any unscheduled endoscopic procedures performed during the course of the four-year follow-up. Two central pathologists, blinded to treatment assignment, determined the size, number, location, and histology of all lesions. An adenoma was defined as recurrent if it occurred any time after the one-year colonoscopy or, if that visit was missed, during an endoscopic procedure at least two years after randomization. There were a few colorectal cancers diagnosed, and these were considered recurrent lesions. Adenomas were classified as advanced if they had a maximal diameter of at least 1 cm or at least 25% villous elements or evidence of high-grade dysplasia, including carcinoma. Adenomas were also classified by location, with "proximal" defined as large bowel from the cecum up to, but not including, the splenic flexure; "distal" as the splenic flexure up to, but not including, the rectum; and "distal/rectum" as the previously defined distal portion and the rectum combined. Subjects with multiple polyps could be considered as cases in more than one locational analysis if their polyps were detected in separate, defined intestinal sites. These subjects did not serve as controls in any analysis.

Physical activity and study data

At randomization (T0), and each year throughout the trial (T1–T4), subjects completed an interview-administered modified Block/NCI food-frequency question-

naire, a four-day food record, and a general health and lifestyle questionnaire that included questions on physical activity. Subjects were shown a chart with multiple examples of light, moderate, and vigorous activities, including self-care or home maintenance, occupational, and recreational/exercise types of activities. They were then asked how much time during the past year they typically spent on weekends and separately, on weekdays, in moderate, and then vigorous activities. Data are expressed in terms of average hours per week spent in moderate or vigorous activities of all types. To examine total time spent in moderate and vigorous activity with consideration for intensity level, an index was created using the relative MET (metabolic equivalent unit) values for moderate and vigorous activities [20]. MET values of 4.5 for moderate and 6.0 for vigorous were used to create a weighted score [MET-hours/week = (hours/week moderate activity $\times$ 4.5) + (hours/week vigorous activity $\times$ 6.0). For the analysis of vigorous activity throughout the trial period, categories of never, sometimes, and consistently vigorously active were created for the 1698 people who had physical activity information available for all time points. Participants reporting no vigorous activity at every time point were placed in the ''never'' category. Participants reporting at least 0.75 hour/week at every time point were placed in the ''consistently'' category. All other participants were considered ''sometimes'' active. Weight and height were measured at T0, and weight was measured annually.

Statistical analysis

There appeared to be a difference in the way in which physical activity was assessed by clinical center at T0, so all sites received additional training prior to T1. Consequently, information on physical activity and other covariates reported at one-year post-randomization (T1), was used as the primary activity information for this analysis. Of the 1905 completing the trial, 1839 had information on physical activity at T1 and were included in the current analyses. Statistical analyses were performed using Statistical Analysis Systems (SAS) software (SAS Institute, Cary, NC). Differences in characteristics of the participants by level of physical activity at T1 were examined using a test for trend in the mean values of the continuous variables, and by chi-square test for categorical variables. The Hotelling T2 test was used to compare the differences in moderate and vigorous activity between the control and intervention groups. This multivariate *t*-test compares the mean vectors across the two groups and results in a single global test for all the points. The data points used were T2–T1, T3–T1, and T4–T1. Because this test requires an equal number of data points at each time period, the sample was limited to those participants with data at all four data collection periods (n = 1698). Differences at each year in the trial were also examined using *t*-tests.

Logistic regression models were used to estimate the odds ratio (OR) and 95% confidence intervals (CI) of adenoma recurrence associated with physical activity level. Age; intervention group; clinical center; weight; body mass index (BMI); education; smoking; nonsteroidal anti-inflammatory (NSAID) use; estrogen use; presence of multiple polyps at baseline colonoscopy (T0); and daily intake of total energy, fat, fiber, fruit and vegetables, alcohol, and calcium were assessed as potential confounders of the associations in men and women separately, and also for each of the types of activity examined. Those variables that changed the risk estimates by more than 10% were included in the models. Covariate adjustment differed by sex. Regression models for the women included terms for age, intervention group, and clinical center, while models for the men adjusted only for age. Because there was some suggestion of a difference in response to the intervention in men and women, models that included both men and women were adjusted for age, intervention group, clinical center, sex, and the sex*intervention group interaction. Models in which moderate activity was examined separately excluded subjects who reported any vigorous activity. Effect modification by BMI; body weight; NSAID use; presence of multiple or advanced polyps at baseline; and dietary fiber, calcium, fat, and fruit and vegetables was examined by including cross-product terms of each variable with vigorous physical activity in separate models. Separate models were also run looking at the recurrence of advanced and multiple polyps, and also by anatomic location of the recurrent polyp. For all these analyses only those with no polyp recurrence were included in the reference group (*e.g.* proximal colon polyp recurrence *vs* no polyp recurrence).

Results

Of the 1839 participants with T1 physical activity information, 65% were men, and 11% were from minority races or ethnic groups. The overall recurrence rate was 40%. These sex, race, and recurrence rate statistics were comparable to those of the 1905 who completed the trial (64% men, 10% minorities, 39% recurrence rate). The characteristics by level of physical activity in men and women participants who completed the study are shown in Table 1. Among the women, age varied inversely with activity level, while dietary intake of fiber, fruit and vegetables, and calcium was highest

Table 1. Characteristics of women and men in PPT by quartile of physical activity in MET-hours/week[a,b,c]

(a) Women

Variable	MET-hours/week quartiles				*p*-Value[d]
	0–11.5 (6.4) n = 161	11.6–23.5 (17.0) n = 160	23.6–44.9 (32.4) n = 164	45.0–483 (70.8) n = 162	
Age (years)	62.5 ± 9.8	60.6 ± 11.4	58.6 ± 10.4	57.5 ± 10.4	<0.001
Weight (kg)	70.8 ± 12.2	70.9 ± 13.7	69.9 ± 12.0	68.6 ± 11.9	0.07
BMI (kg/m^2)	27.2 ± 4.5	27.0 ± 4.8	26.5 ± 4.4	25.9 ± 4.2	0.004
Energy intake (kcal/day)	1583 ± 417	1649 ± 417	1637 ± 412	1676 ± 415	0.09
Fat (g/day)	53.7 ± 24.3	57.0 ± 23.2	52.4 ± 20.9	52.4 ± 23.6	0.27
Fiber (g/day)	21.3 ± 10.5	21.9 ± 10.9	23.8 ± 11.4	24.9 ± 12.4	0.003
Fruit and vegetables (g/day)	697 ± 328	745 ± 381	800 ± 400	827 ± 384	0.005
Alcohol (servings/week)	1.2 ± 3.1	2.0 ± 3.7	2.5 ± 4.3	2.2 ± 3.7	0.07
Calcium (mg/day)	1072 ± 762	1112 ± 714	1191 ± 801	1294 ± 827	0.006
% ≤ HS education	37.3	26.3	26.8	26.5	0.16
% Current smokers	13.7	14.4	12.2	16.7	0.71
% Current NSAID use	39.8	37.5	32.9	30.3	0.27
% Current estrogen use	34.8	37.5	37.2	38.3	0.82

(b) Men

Variable	MET-hours/week quartiles				*p*-Value
	0–18.8 (10.9) n = 298	18.9–37.4 (28.1) n = 296	37.5–67.5 (50.6) n = 301	67.6–486 (113.6) n = 297	
Age (years)	63.1 ± 9.8	61.6 ± 9.5	61.9 ± 9.1	60.7 ± 8.8	0.005
Weight (kg)	86.7 ± 13.7	85.6 ± 12.4	86.2 ± 13.2	86.2 ± 12.6	0.88
BMI (kg/m^2)	27.8 ± 3.8	27.5 ± 3.6	27.4 ± 3.6	27.5 ± 3.6	0.50
Energy intake (kcal/day)	1908 ± 489	1914 ± 494	1947 ± 500	2072 ± 566	<0.001
Fat (g/day)	66.3 ± 28.9	65.1 ± 27.5	61.0 ± 25.8	68.4 ± 30.5	0.20
Fiber (g/day)	24.1 ± 12.8	24.8 ± 12.8	28.0 ± 14.9	27.7 ± 14.2	<0.001
Fruit and vegetables (g/day)	704 ± 354	751 ± 349	828 ± 402	824 ± 416	<0.001
Alcohol (servings/week)	4.0 ± 6.0	4.4 ± 6.8	4.6 ± 7.1	4.5 ± 6.3	0.41
Calcium (mg/day)	918 ± 456	1000 ± 658	1004 ± 580	994 ± 524	0.26
% ≤ HS education	25.6	18.9	20.9	22.6	0.17
% Current smokers	16.8	10.8	11.3	10.8	0.07
% Current NSAID use	30.2	37.8	38.9	38.0	0.10

[a] MET = metabolic equivalent unit. Calculated for reported hours of moderate and vigorous activity. Quartiles presented as range (median).
[b] Values presented as mean ± SD or percent of quartile.
[c] Abbreviations used: BMI, body mass index; HS, high school; NSAID, non-steroidal anti-inflammatory.
[d] *p*-Values were calculated by the test for trend in means across physical activity quartiles for the continuous variables, and by chi-square tests for categorical variables.

among the most active. The more active women also tended to have lower BMIs. Surprisingly, the most active women reported the highest current smoking level. In the men, neither body weight nor body mass index (BMI) appeared to vary much with level of physical activity as it did in the women. The more active men were younger and reported higher dietary intakes of total energy, fiber and fruit and vegetables. In contrast to the women, the current smoking level was highest among the least active men.

The associations between T1 physical activity and overall polyp recurrence in men and women separately, and in men and women combined, are shown in Table 2. There were no associations found in any of the groups for the MET-hours/week index, weekly hours of vigorous activity, or weekly hours of moderate activity among the 66% of women and 46% of men who reported no vigorous activity. There was no evidence of effect modification of the vigorous activity and polyp recurrence relationship by a number of potential risk factors for recurrence (*i.e.* multiple or advanced polyps at baseline (T0) colonoscopy, dietary fiber, calcium, fat, fruit and vegetables, BMI, body weight, and NSAID use) ($p > 0.05$).

Since activity information was updated on an annual basis we sought to determine whether reported hours of physical activity changed across the trial period (Table 3). The multivariate Hotelling T2 test which compares the mean vectors at T2–baseline, T3–baseline,

Table 2. Association between measures of physical activity and overall polyp recurrence in women, men, and in all participants combined[a,b]

Moderate and vigorous activity			Vigorous activity			Moderate activity[d]		
MET-hour/week[c] Range (median)	Cases/ non-cases	OR (CI)	Hour/week range (median)	Cases/ non-cases	OR (CI)	Hour/week range (median)	Cases/ non-cases	OR (CI)
Women								
0–11.5 (6.4)	58/103	1.0	0	142/276	1.0	0–2.0 (1.0)	38/65	1.0
11.6–23.5 (17.0)	48/112	0.9 (0.6–1.5)	0.01–0.7 (0.2)	35/79	0.9 (0.5–1.4)	2.1–4.1 (3.3)	35/71	1.0 (0.5–1.8)
23.6–44.9 (32.4)	49/115	1.0 (0.6–1.6)	0.71–40 (2.2)	26/89	0.7 (0.4–1.2)	4.2–8.0 (5.7)	39/66	1.3 (0.7–2.3)
45.0–483 (70.8)	48/114	1.0 (0.6–1.6)				8.1–68 (12.0)	30/74	0.9 (0.5–1.7)
p-Trend		0.96			0.20			0.75
Men								
0–18.8 (10.9)	121/177	1.0	0	254/290	1.0	0–2.5 (0.9)	62/74	1.0
18.9–37.4 (28.1)	137/159	1.3 (0.9–1.8)	0.01–0.62 (0.25)	106/110	1.1 (0.8–1.6)	2.6–5.1 (3.8)	58/78	0.9 (0.5–1.4)
37.5–67.5 (50.6)	135/166	1.2 (0.9–1.7)	0.63–2.48 (1.28)	82/133	0.8 (0.6–1.1)	5.2–10.0 (7.5)	66/71	1.1 (0.7–1.8)
67.6–486 (113.6)	137/160	1.3 (1.0–1.9)	2.5–52.5 (5.0)	88/129	0.9 (0.6–1.2)	10.1–84.2 (16.2)	68/67	1.2 (0.8–2.0)
p-Trend		0.20			0.30			0.26
All								
0–15.7 (8.3)	171/288	1.0	0	396/566	1.0	0–2.25 (0.9)	101/140	1.0
15.8–32.6 (23.3)	186/274	1.2 (0.9–1.6)	0.01–0.52 (0.23)	120/172	1.0 (0.8–1.3)	2.3–4.7 (3.5)	89/150	0.9 (0.6–1.3)
32.7–59.2 (42.9)	179/282	1.1 (0.8–1.4)	0.53–2.16 (1.11)	107/185	0.8 (0.6–1.1)	4.8–9.1 (6.5)	98/143	1.0 (0.7–1.4)
59.3–486 (100.1)	197/262	1.2 (0.9–1.6)	2.17–52.5 (4.5)	110/183	0.9 (0.7–1.2)	9.2–84.2 (14.7)	108/133	1.1 (0.8–1.6)
p-Trend		0.25			0.32			0.34

[a] Association expressed as odds ratio (OR) and 95% confidence interval (CI).

[b] Models in women adjusted for age, intervention group, and clinical center. Models in men adjusted for age. Models in both women and men adjusted for age, clinical center, sex, intervention group, and sex*intervention group interaction.

[c] MET = metabolic equivalent unit. Calculated for reported hours of moderate and vigorous activity.

[d] Analysis of moderate activity restricted to persons reporting no vigorous activity.

Table 3. Hours per week (mean ± standard deviation) of moderate and vigorous activity by intervention group and study time-point[a]

Group	T1	T2	T3	T4
Moderate[b]				
Control	9.4 ± 10.8	9.0 ± 9.3	8.8 ± 9.5	8.8 ± 9.4
Intervention	9.1 ± 9.3	8.8 ± 9.1	9.0 ± 9.2	9.1 ± 9.6
Vigorous[c]				
Control	1.1 ± 2.9	1.1 ± 2.9	1.2 ± 3.6	1.2 ± 3.0
Intervention	1.5 ± 3.9	1.4 ± 4.4	1.1 ± 3.0	1.3 ± 3.0

[a] For subjects with complete information throughout the trial period: n = 855, control; n = 843, intervention.
[b] Across the trial, no difference between groups (Hotelling T2, $p = 0.82$).
[c] Across the trial, no difference between groups (Hotelling T2, $p = 0.06$); T1 time-point (t-test, $p = 0.03$).

and T4–baseline across the two groups showed no significant differences between the control and intervention groups for either moderate ($p = 0.82$) or vigorous ($p = 0.06$) activity. A t-test at each year showed a significant difference ($p = 0.03$) for vigorous activity at T1, but not for subsequent years. We then examined the risk of recurrence based on reported activity levels throughout the trial among the 1689 participants with complete physical activity information at all time-points. The recurrence rate among this subset of the PPT was 40%, as in the whole cohort. Given similarities in risk estimates between the men and women for overall recurrence and vigorous activity, the combined data are presented in Table 4. There was no significantly lower risk of overall recurrence for participants who reported being either consistently or sometimes active compared to those who never reported vigorous activity, nor was there a difference in the recurrence of advanced adenomas. There was a non-significant 50% reduction in risk of multiple polyps in the consistently active compared to the never active group (OR = 0.5, CI = 0.3–1.0). No significant associations were seen for proximal, distal, or distal/rectal polyp recurrence.

Discussion

This is the first study that was able to examine the association between physical activity and adenomatous polyp recurrence prospectively, because subjects were participating in a randomized clinical trial designed to look specifically at polyp recurrence. The only other study to date that has examined polyp recurrence did so retrospectively, using a case–control design. Neugut *et al.* [13] compared 197 subjects with metachronous adenomas with 345 subjects with normal colonoscopies who had a prior history of adenomas. The odds ratio for any physical activity in the past year compared to none was 0.6 (0.3–1.0) in the men, and 1.0 (0.4–2.6) in the women. The definition of "any physical activity" used in the study by Neugut *et al.* corresponded to ~5 hours/week or more of vigorous activity. This value is equal to the median value for our highest quartile of vigorous activity in men, for which we found no association with polyp recurrence. All other prior studies have looked at colorectal adenomas prevalent at screening. Of the two prospective studies reported to date, one saw no significant reduction in risk for adenomas in men [10],

Table 4. Association between vigorous physical activity throughout the trial period, and overall recurrence, recurrence of advanced or multiple polyps, and recurrence by anatomical location in all participants combined[a,b,c]

Vigorous activity[d]	Overall recurrence	Advanced polyps	Multiple polyps	Proximal polyps	Distal polyps	Distal/rectal polyps
Never	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Sometimes	1.0 (0.8–1.3)	0.8 (0.5–1.3)	0.9 (0.7–1.3)	1.2 (0.9–1.6)	0.8 (0.5–1.2)	0.8 (0.5–1.2)
Consistently	0.8 (0.5–1.1)	0.9 (0.4–2.1)	0.5 (0.3–1.0)	1.0 (0.6–1.7)	0.7 (0.4–1.5)	0.6 (0.3–1.2)
No. of cases/controls	679/1019	110/1019	288/1019	337/1019	153/1019	194/1019
p-Trend	0.31	0.57	0.13	0.68	0.28	0.12

[a] Association expressed as relative risk (RR) and 95% confidence interval (CI).
[b] Models adjusted for age, clinical center, sex, intervention group, and sex*intervention group interaction.
[c] Analysis limited to participants with complete physical activity information throughout the trial (n = 1698).
[d] Participants classified as never vigorously active consistently reported 0 hour/week of vigorous activity. To be classified as consistently vigorously active, participants reported at least 0.75 hour/week of vigorous activity at each phase of the trial. The "sometimes" category includes people who were not consistent in regard to their vigorous physical activity habits across phases.

and the other saw a 42% lower risk among women engaging in the highest levels of physical activity [12]. Both of these cohort studies were limited to the distal colon due to the use of sigmoidoscopies for screening. Case–control studies of adenomas have been more consistent in demonstrating lower risks in the active individuals [6–9, 11, 13, 14].

The few studies that have examined exercise in the prevention of polyp development in animal models have reported disparate results. Rat models of chemically induced carcinogenesis have demonstrated both a reduction [21] and no effect of exercise [22] on adenoma development in the colon. Moderate exercise has been found to only modestly reduce polyp number in male, but not female, induced-mutant mice (APC^{Min} mice), predisposed to adenomatous polyp development [23].

The lack of association between physical activity and overall polyp recurrence seen in this study may have several possible explanations. Measurement error associated with the assessment of physical activity may weaken our ability to precisely estimate the association. Our data suggested that body weight in the men, and smoking activity in the women, did not vary with reported physical activity as might be expected, which could indicate some error in our classification. We also examined past year physical activity throughout the trial, and it may be that recent/current physical activity has no effect on polyp recurrence. Perhaps it is longer-term or earlier lifetime activity that is associated with any beneficial affect on polyps, and the three-year follow-up time in our study was too short to see any associations. Indeed, the low-fat, high fiber dietary intervention tested in PPT did not reduce the rate of polyp recurrence in these participants [19]. It should be noted, however, that a short-term calcium intervention has been found to reduce polyp recurrence [24] and, in an observational epidemiologic analysis that combined intervention and control group participants within the PPT, NSAID use was found to be associated with reduced polyp recurrence (J. Tangrea, personal communication). Certainly the effective periods of various physiologic and/or pharmacologic exposures may differ. Alternatively, it may be that persons who are ''polyp producers,'' who have a large rate of recurrence [25], are not benefited by a physically active lifestyle. Clearly our subjects were predisposed to polyp development; therefore they may be a population for whom physical activity would have little or no effect. Given that physical activity has been consistently associated with a lower risk of colon cancer [2], it is puzzling that the same association was not seen with adenoma formation here. Perhaps activity is important in the adenoma to carcinoma sequence and not in the prevention of adenoma development. Some studies of exercise in chemically induced rat models of colon carcinogenesis have reported a decrease in adenocarcinomas and carcinomas but not adenomas [22, 26]. However, if activity inhibited progression we might have expected to see a reduced risk of recurrence of advanced polyps, which we did not. Finally, we may have had too few people who were consistently active in our study population to obtain a precise estimate of the association. Within our cohort only 9% of our population were consistently vigorously active throughout the trial, and that was with a generous definition of consistently active of only 0.75 hour/week of vigorous activity. Protective associations between physical activity and colon cancer have been seen for higher levels of moderate to vigorous activity [27]; however, using our T1 data (Table 2), we still did not see associations with polyp recurrence for higher reported weekly hours of vigorous activity ($\sim$4.5 hours/week).

A strength of our study is the prospective design, in which complete cleaning colonoscopies were performed prior to interviewer-administered, annual assessment of total physical activity. Certain limitations to our study design, however, must be considered. The subjects in our study were participants in a clinical trial, and so may not be representative of the general population. Upon diagnosis of their first polyp prior to randomization in the study, subjects may have changed their activity habits; however, we observed no change in the average reported activity level across the 4 years of the study. Our data are limited to past year assessments of physical activity. If it is activity earlier in life that affects the development of polyps, we may have missed the critical time period of inquiry. Further, the trial was not designed to examine the effect of physical activity on polyp recurrence. In this trial the physical activity was assessed primarily to be included in analyses to examine potential confounding of the primary exposure of interest to the trial, diet and polyp recurrence. Although subjects were asked to report hours of activity of many types using lists of various activities as examples, our questionnaire was limited, as participation in specific activities was not individually queried. Additionally, not many of the participants in this study were found to be consistently vigorously active, decreasing our ability to examine recurrence based on consistency of activity. Finally, conclusions can only be drawn for the recurrence of polyps, not the incidence of polyps in those who have no previous diagnosis of colorectal adenomas. The PPT subjects would not be an appropriate group to examine if activity is only important in the preclinical development of polyps.

Our data suggest that physical activity, regardless of intensity, is not associated with a reduced risk of polyp

recurrence for both men and women. Potential risk factors for polyp development, including body weight or size, diet, NSAID use, and multiple or advanced polyps at baseline did not modify the associations. When we further looked at the association by anatomic site of recurrence or for the recurrence of advanced polyps, again there was no association, although there was some suggestion that higher levels of activity were associated with a lower risk of developing multiple polyps. Finally, taking into consideration the activity levels of the men and women throughout the trial did not change the association with polyp recurrence, such that even those consistently participating in vigorous activity had no significantly lower risk compared to those who were consistently sedentary. Despite these findings, physical activity should still be encouraged among those with a history of polyps, as no adverse association was noted, and particularly for the myriad of other health benefits that have been associated with a physically active lifestyle, including a reduced risk of colon cancer.

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